Intramolecular Ring-Ring Stacking Interactions between 8-Methoxypsoralen and Adenine Induced by Polymethylene Bridges

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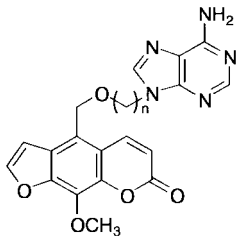
Intramolecular ring-ring interactions in the model compounds, 8-methoxypsoralen-$CH_2O(CH_2)_n$-adenine ($MOPCH_2OCnAd$, n=2, 3, 5, and 6) in which 5' position of 8-methoxypsoralne (8-MOP) is linked by different polymethylene bridges to N^9 of adenine, have been investigated by hypochromism measurements. Efficient ring-ring stacking interactions have been observed in $MOPCH_2OC2Ad$ (**7**) from the percent hypochromism (%H) and fluorescence spectra of the models and a reference molecule. The 8-methoxypsoralen-adenine systems have shown stronger ring-ring stacking interaction than the psoralen-adenine systems.

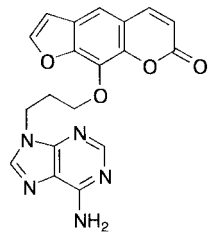
Keywords : Psoralen, 8-Methoxypsoralen, Ring-ring stacking interactions, Percent hypochromism (%H).

Introduction

PUVA therapy,[1-4] a photochemotherapy employing psoralen and UVA, has been used for a long time in the treatment of a number of skin disorders, such as psoriasis, vitiligo, mycosis fungoides, chromic leukemia, and so on.[5-8] In addition to medicinal applications, psoralens have been used as molecular probes in elucidating structures of many important biological macromolecules.[9,10] A large number of studies on the mechanism of the photochemical reactions between psoralen and DNA bases *in vivo* or with thymine derivatives have been carried out. These studies involved intermolecular processes leading generally to a mixture of several photoproducts. The interactions between psoralens and DNA take place in two steps: (a) formation of molecular complexes (intercalation) in the ground state; (b) covalent photobinding of complexed psoralens to pyrimidine bases of DNA.[1,11,12] Intercalation occurs preferentially in the regions having an alternate sequence of purines and pyrimidines, and these regions are also preferred for covalent photobinding, in particular the alternate sequence of adenine and thymine. The formation of the intercalated complex between psoralens and DNA is an important step, which markedly affects the successive covalent photobinding to the macromolecule. In order to investigate these processes, some of synthetic models related to DNA-intercalating molecules were prepared and studied.[13-17] Decout et al. prepared a series of PsOCnAd (n=3, **11**) and showed that the polymethylene bridges allow intramolecular ring-ring stacking between the two aromatic units.[15] Recently, Shim *et al.* suggested that the photoreaction of psoralens with DNA proceeds by adenosine-mediated electron transfer from/to psoralens to/from thymine base.[18] In order to elucidate the role of adenine ring in the complexation process, we have prepared new model structures $MOPCH_2OCnAd$ (**7**-**10**), geometrically different from PsOCnAd series, in which 5' site of 8-methoxypsoralen (8-MOP, **1**) is linked to N^9 of adenine base by flexible polymethylene chains of varying length. Herein, we compare the difference of intramolecular ring-ring stacking interactions between psoralen-adenine pair (PsOCnAd) and 8-methoxypsoralen-adenine systems ($MOPCH_2OCnAd$).



$MOPCH_2OCnAd$ (**7**-**10**)



PsOC3Ad (**11**)

Materials and Methods

Instruments. The ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on Brüker AM-400 MHz spectrometers. Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS), and ^{13}C resonances were recorded using the 77.0 ppm $CDCl_3$ resonance peak of the solvent as an internal reference and reported in ppm downfield from TMS. Fourier transform

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<*Abbreviations*> AdC3, adenine-$(CH_2)_3$; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; EI, electron impact; FTIR, Fourier transform infrared; HRMS, high resolution mass spectroscopy; HPLC, high-performance liquid chromatography; 8-MOP, 8-methoxypsoralen; $MOPCH_2OC3$, 8-methoxypsoralen-$CH_2O(CH_2)_3$; $MOPCH_2OCnAd$, 8-methoxypsoralen-$CH_2O(CH)_n$-adenine; NMR, nuclear magnetic resonance; O.D., optical density; %H, percent hypochromism; Ps, psoralen; PUVA, psoralen+UVA; TMS, tetramethylsilane; UV, ultraviolet; UVA, 320-400 nm radiation.

infrared (FTIR) spectra were recorded on a Bomem MB-100 Series FTIR spectrophotometer. Mass spectra were determined at 70 eV with V.G. AutoSpec Ultma by the electron impact (EI) method. Melting points were determined in capillary tubes on a Thomas Hoover capillary melting point apparatus. UV absorption spectra were recorded on a Shimadzu 31000S spectrophotometer. Fluorescence spectra were recorded on a Perkin-Elmer LS-50 luminescence spectrometer with a gated photomultiplier tube detector at room temperature.

Materials and syntheses. 8-MOP was obtained from Sigma Chemical Co. and purified by recrystallization from methanol. All the solvents were reagent grade or high-performance liquid chromatography (HPLC) grade and purified according to the literature procedure.[19] Spectroscopic grade ethanol was purchased from Merck and used as received. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used as analytical TLC. Gravity column chromatography and flash chromatography were carried out on silica gel (230-400 mesh from Merck). Individual 8-methoxypsoralen-$CH_2O(CH_2)_n$-adenine (MOPCH$_2$OCnAd, n=2, 3, 5, and 6) and reference compounds (Figure 1) were synthesized as follows: The reference molecule (**2**) was prepared by the alkylation of adenine with bromopropane under potassium carbonate base in the presence of catalytic amount of potassium iodide.[20] Chloromethylation of 8-MOP (**1**) at C-5 position with chloromethylethyl ether afforded 5-chloromethyl-8-methoxypsoralen **4** in 90% yield by the known procedure.[21] The other reference compound (**3**) was also prepared by the alkylation of the intermediate (**4**) with 1-propanol. The model compounds (**7**-**10**, MOPCH$_2$OCnAd)

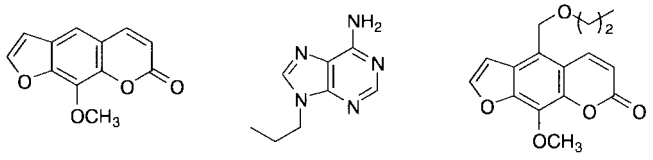
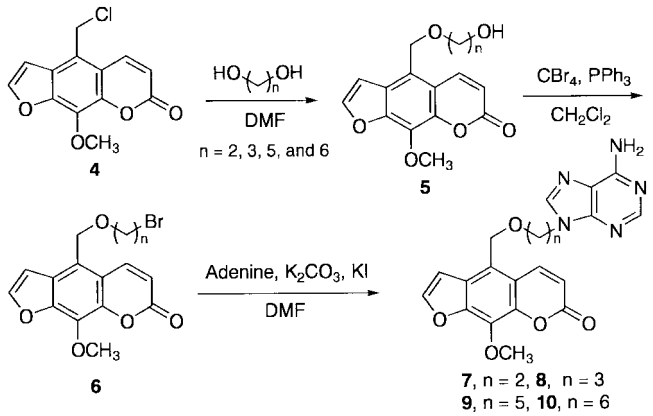


Figure 1. Chemical structures of 8-MOP (**1**), AdC3 (**2**) and MOPCH$_2$OC3 (**3**).



Scheme 1. Syntheses of the model compounds, MOPCH$_2$OCnAd (**7**-**10**).

were prepared through three steps as described in Scheme 1. Alcohol compounds (**5a**-**5d**) were obtained by the reaction of **4** with α,ω-alkanediol as described for the preparation of **3**.[22] An improved yield was obtained by reacting **4** with α,ω-alkanediol in DMF at 90-100 °C. Bromination of alcohol compounds **5a**-**5d** with carbon tetrabromide and triphenyl phosphine in methylene chloride afforded compounds **6a**-**6d**.[23] Target molecules (**7**-**10**) were successfully synthesized by nucleophilic displacement coupling reaction of **6a**-**6d** with adenine in DMF (K_2CO_3).[20]

Preparation of AdC3 (2). *n*-Propylbromide (0.44 g, 3.6 mmol) was stirred at room temperature in DMF (10 mL) with adenine (0.41 g, 3.0 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and KI (50.0 mg, 0.3 mmol) for 2 days. The mixture was filtered, and the inorganic material was washed with 20% ethanol in methylene chloride. Following removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (eluent: 10% ethanol in methylene chloride) to yield 0.41 g (78%) of the compound **2** as a white solid: mp 173-174.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 (t, 3H, J = 7.4 Hz), 1.80 (m, 2H), 3.32 (s, NH$_2$), 4.08 (t, 2H, J = 6.9 Hz), 7.16 (bs, 1H), 8.12 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.88, 22.71, 44.45, 118.72, 140.84, 149.54, 152.30, 155.85, 155.91; HRMS: calcd for $C_8H_{10}N_5$: 177.1014, found: 177.1022.

Preparation of MOPCH$_2$OC3 (3). A mixture of the 5-(chloromethyl)-8-methoxypsoralen (**4**) (0.22 g, 0.83 mmol) and 1-propanol (1.75 g, 29.1 mmol) was heated at 95-100 °C with stirring for 12 hr and cooled to room temperature. The resulting mixture was concentrated and chromatographed with 25% ethyl acetate in hexane to give alcohol **3** (0.22 g, 90%) as a white solid: mp 70-72.5 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, 3H, J = 7.4 Hz), 1.60 (m, 2H), 3.44 (t, 2H, J = 6.6 Hz), 4.26 (s, 3H), 4.83 (s, 2H), 6.38 (d, 1H, J = 9.9 Hz), 6.92 (d, 1H, J = 2.2 Hz), 7.66 (d, 1H, J = 2.2 Hz), 8.23 (d, 1H, J = 9.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 10.62, 22.89, 61.33, 66.44, 72.39, 105.45, 114.58, 115.29, 120.72, 126.50, 132.56, 141.18, 143.76, 146.48, 146.97, 160.17; HRMS: calcd for $C_{16}H_{16}O_5$: 288.0998, found: 288.0998.

Preparation of MOPCH$_2$OC2OH (5a). 5-Chloromethyl-8-methoxypsoralen (**4**) (0.75 g, 2.83 mmol) was mixed with 1,2-ethanediol (10 mL) and heated to 90-100 °C with stirring for 12 hr and cooled to room temperature. The resulting mixture was concentrated and column chromatographed with 50% ethyl acetate in hexane to give alcohol **5a** (0.53 g, 68%) as a white solid: mp 142 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.01 (bs, 1H, OH), 3.59-3.61 (m, 2H), 3.73 (t, 2H, J = 4.3 Hz), 4.26 (s, 3H), 4.26 (s, 3H), 4.91 (s, 2H), 6.39 (d, 1H, J = 9.8 Hz), 6.93 (d, 1H, J = 2.3 Hz), 7.68 (d, 1H, J = 2.3 Hz), 8.12 (d, 1H, J = 9.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 61.33, 61.87, 66.74, 71.57, 105.33, 114.89, 115.37, 119.93, 126.68, 132.80, 140.86, 143.73, 146.69, 146.92, 160.03; HRMS Calcd for $C_{15}H_{14}O_6$: 290.0790, found: 290.0795.

Preparation of MOPCH$_2$OC3OH (5b). Reaction of 5-chloromethyl-8-methoxypsoralen (**4**) (0.64 g, 2.42 mmol) and 1,3-propanediol (10 mL) as described for the preparation of **5a** yielded 0.52 g (70.6%) of alcohol **5b** as a white

solid: mp 103.5-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-1.85 (q, 2H), 2.10 (bs, 1H, OH), 3.64 (t, 2H, J = 6.0 Hz), 3.82 (t, 2H, J = 5.7 Hz), 4.25 (s, 3H), 4.85 (s, 2H), 6.39 (d, 1H, J = 9.8 Hz), 6.92 (d, 1H, J = 2.3 Hz), 7.67 (d, 1H, J = 2.3 Hz), 8.11 (d, 1H, J = 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.21, 60.90, 62.05, 66.63, 68.79, 105.33, 114.76, 115.30, 120.12, 126.64, 132.72, 140.91, 143.68, 146.64, 146.91, 160.13; IR (cm^{-1}) 3415, 3112, 2952, 2871, 1729, 1587, 1481, 1420, 1387, 1313, 1132, 1093, 1038, 831, 762; HRMS Calcd for $C_{16}H_{16}O_6$: 304.0947, found: 304.0956.

Preparation of MOPCH$_2$OC5OH (5c). Reaction of 5-chloromethyl-8-methoxypsoralen (**4**) (0.82 g, 3.08 mmol) and 1,5-pentanediol (10 mL) as described for the preparation of **5a** yielded 0.63 g (61.3%) of alcohol **5c** as a white solid: 76-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.39 (q, 2H), 1.48-1.53 (q, 2H), 1.55-1.61 (q, 2H), 3.47 (t, 2H, J = 6.4 Hz), 3.57 (t, 2H, J = 6.4 Hz), 4.23 (s, 3H), 4.81 (s, 2H), 6.36 (d, 1H, J = 9.9 Hz), 6.91 (d, 1H, J = 2.3 Hz), 7.66 (d, 1H, J = 2.3 Hz), 8.12 (d, 1H, J = 9.9 Hz); ^{13}H NMR (100 MHz, $CDCl_3$) δ 22.37, 29.37, 32.31, 61.30, 62.60, 66.44, 70.56, 105.41, 114.55, 115.26, 120.61, 126.53, 132.56, 141.16, 143.70, 146.52, 146.92, 160.18; IR (cm^{-1}) 3429, 3113, 2945, 2864, 1729, 1587, 1481, 1420, 1387, 1313, 1132, 1098, 1044, 829, 762; HRMS Calcd for $C_{18}H_{20}O_6$: 332.1259, found: 332.1254.

Preparation of MOPCH$_2$OC6OH (5d). Reaction of 5-chloromethyl-8-methoxypsoralen (**4**) (0.70 g, 2.65 mmol) and 1,5-hexanediol (10 mL) as described for the preparation of **5a** yielded 0.65 g (71.1%) of alcohol **5d** as a white solid: mp 98-100.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.33 (m, 4H), 1.49-1.59 (m, 5H), 3.46 (t, 2H, J = 6.5 Hz), 3.58 (t, 2H, J = 6.5 Hz), 4.24 (s, 3H), 4.82 (s, 2H), 6.37 (d, 1H, J = 9.9 Hz), 6.91 (d, 1H, J = 2.3 Hz), 7.66 (d, 1H, J = 2.3 Hz), 8.12 (d, 1H, J = 9.9 Hz); ^{13}H NMR (100 MHz, $CDCl_3$) δ 25.47, 25.93, 29.60, 32.58, 61.30, 62.74, 66.44, 70.58, 105.42, 114.54, 115.27, 120.67, 126.52, 132.56, 141.16, 143.73, 146.49, 146.95, 160.17; IR (cm^{-1}) 3431, 3116, 2929, 2864, 1726, 1592, 1478, 1418, 1384, 1311, 1132, 1088, 1040, 831, 753; HRMS Calcd for $C_{19}H_{22}O_6$: 346.1416, found: 346.1418.

Preparation of MOPCH$_2$OC2Br (6a). To a magnetically stirred solution of **5a** (0.33 g, 1.14 mmol) and carbon tetrabromide (0.74 g, 2.25 mmol) in methylene chloride (20 mL) was added triphenylphosphine (0.62 g, 2.36 mmol) portionwise with ice-bath cooling. Upon completion of the reaction, ice-water (50 mL) was added and the oily suspension was extracted with methylene chloride. The organic extract was dried with magnesium sulfate, and the solvent was removed *in vacuo*. The resulting material was dissolved in ethyl acetate and subjected to column chromatography on silica gel with 30% ethyl acetate in hexane which gave compound **6a** (0.37 g, 92.2%) as a white solid: mp 117-118.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 2H), 3.45 (t, 2H, J = 6.0 Hz), 3.80 (t, 2H, J = 6.0 Hz), 4.26 (s, 3H), 4.93 (s, 2H), 6.40 (d, 1H, J = 9.9 Hz), 6.94 (d, 1H, J = 2.3 Hz), 7.68 (d, 1H, J = 2.3 Hz), 8.17 (d, 1H, J = 9.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.39, 61.34, 66.70, 70.15, 105.32, 114.87, 115.40, 119.44, 126.66, 132.85, 141.07, 143.72, 146.72, 146.84, 160.07; HRMS Calcd for $C_{15}H_{13}BrO_5$: 351.9946, found: 351.9923.

Preparation of MOPCH$_2$OC3Br (6b). Reaction of **5b** (0.59 g, 1.95 mmol), carbon tetrabromide (1.29 g, 3.89 mmol), and triphenylphosphine (1.07 g, 4.09 mmol) was carried out as described for the preparation of **6a** to obtain **6b** (0.67 g, 93.4%): mp 57-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03-2.09 (q, 2H), 3.44 (t, 2H, J = 6.3 Hz), 3.62 (t, 2H, J = 5.7 Hz), 4.24 (s, 3H), 4.84 (s, 2H), 6.38 (d, 1H, J = 9.9 Hz), 6.92 (d, 1H, J = 2.2 Hz), 7.67 (d, 1H, J = 2.2 Hz), 8.10 (d, 1H, J = 9.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.38, 32.42, 61.28, 66.60, 67.63, 105.30, 114.70, 115.32, 120.12, 126.61, 132.68, 140.98, 143.67, 146.62, 146.86, 160.05; IR (cm^{-1}) 3113, 2952, 2864, 1726, 1590, 1480, 1424, 1387, 1313, 1135, 1098, 1038, 830, 756; HRMS Calcd for $C_{16}H_{15}BrO_5$: 366.0102, found: 366.0116.

Preparation of MOPCH$_2$OC5Br (6c). Reaction of **5c** (0.61 g, 1.84 mmol), carbon tetrabromide (1.22 g, 3.68 mmol), and triphenylphosphine (1.01 g, 3.87 mmol) was carried out as described for the preparation of **6a** to obtain **6c** (0.62 g, 85.3%) as a white solid: mp 58.5-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.48 (q, 2H), 1.56-1.61 (q, 2H), 1.78-1.85 (q, 2H), 3.35 (t, 2H, J = 6.7 Hz), 3.48 (t, 2H, J = 6.4 Hz), 4.25 (s, 3H), 4.83 (s, 2H), 6.39 (d, 1H, J = 9.9 Hz), 6.92 (d, 1H, J = 2.2 Hz), 7.67 (d, 1H, J = 2.2 Hz), 8.12 (d, 1H, J = 9.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.86, 28.82, 32.39, 33.56, 61.33, 66.51, 70.29, 105.40, 114.67, 115.30, 120.50, 126.52, 132.63, 141.06, 143.76, 146.53, 146.95, 160.10; IR (cm^{-1}) 3116, 2941, 2864, 1729, 1587, 1476, 1423, 1379, 1311, 1132, 1093, 1038, 831, 758; HRMS Calcd for $C_{18}H_{19}BrO_5$: 394.0415, found: 394.0418.

Preparation of MOPCH$_2$OC6Br (6d). Reaction of **5d** (0.62 g, 1.78 mmol), carbon tetrabromide (1.18 g, 3.57 mmol), and triphenylphosphine (0.98 g, 3.75 mmol) was carried out as described for the preparation of **6a** to obtain **6d** (0.58 g, 78.9%) as a white solid: mp 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.45 (m, 4H), 1.54-1.60 (q, 2H), 1.79-1.82 (q, 2H), 3.36 (t, 2H, J = 6.8 Hz), 3.47 (t, 2H, J = 6.4 Hz), 4.26 (s, 3H), 4.83 (s, 2H), 6.39 (d, 1H, J = 9.9 Hz), 6.92 (d, 1H, J = 2.4 Hz), 7.67 (d, 1H, J = 2.4 Hz), 8.12 (d, 1H, J = 9.9 Hz); IR (cm^{-1}) 3075, 2939, 2853, 1729, 1588, 1480, 1424, 1387, 1307, 1165, 1129, 1038, 843, 756; HRMS Calcd for $C_{19}H_{21}BrO_5$: 408.0572, found: 408.0578.

Preparation of MOPCH$_2$OC2Ad (7). Reagent **6a** (0.12 g, 0.35 mmol) was added to a stirred mixture of adenine (56.0 mg, 0.42 mmol), K_2CO_3 (0.11 g, 0.83 mmol), and catalytic amounts of KI (5.0 mg) in DMF (5 mL). The stirring was continued for 72 hr at room temperature. The mixture was filtered and the filter cake was washed with ethyl acetate. Following removal of the solvent *in vacuo*, the residue was chromatographed with 30% ethyl acetate in hexane to give **7** (0.11 g, 78.3%) as a white solid: mp 188-190 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (t, 2H, J = 5.1 Hz), 4.15 (s, 3H), 4.30 (t, 2H, J = 5.1 Hz), 4.91 (s, 2H), 6.27 (d, 1H, J = 9.9 Hz), 7.13 (bs, 2H), 7.19 (d, 1H, J = 2.2 Hz), 7.99 (s, 1H), 8.00 (d, 1H, J = 9.9 Hz), 8.07 (s, 1H), 8.08 (d, 1H, J = 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.84,

60.95, 65.27, 67.34, 105.76, 113.88, 114.91, 118.61, 120.78, 126.49, 131.69, 140.98, 141.70, 142.92, 146.03, 147,67, 149.42, 152.20, 155.85, 159.26; Mass (m/e) 108, 135, 163, 186, 229, 407; HRMS Calcd for $C_{20}H_{17}N_5O_5$: 407.1229, found: 407.1226.

Preparation of MOPCH$_2$OC3Ad (8). Reaction of **6b** (0.50 g, 1.37 mmol), adenine (0.22 g, 1.64 mmol), K_2CO_3 (0.45 g, 3.28 mmol), and catalytic amounts of KI in DMF (15 mL) as described for the preparation of **7** yielded **8** (0.47 g, 81.4%) as a white solid: mp 195-198 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (q, 2H), 3.46 (t, 2H, J = 5.7 Hz), 4.25 (t, 2H, J = 6.7 Hz), 4.27 (s, 3H), 4.81 (s, 2H), 5.80 (bs, 2H), 6.40 (d, 1H, J = 9.9 Hz), 6.91 (d, 1H, J = 2.2 Hz), 7.65 (s, 1H), 7.68 (d, 1H, J = 2.2 Hz), 8.15 (d, 1H, J = 9.9 Hz), 8.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.98, 40.86, 61.33, 66.51, 66.76, 105.23, 114.91, 115.39, 119.63, 119.81, 126.68, 132.83, 140.56, 140.90, 143.70, 146.72, 146.88, 150.15, 152.93, 155.44, 160.03; IR (cm^{-1}) 3335, 3167, 3113, 2932, 2864, 1726, 1649, 1595, 1481, 1418, 1266, 1132, 1036, 827, 755; HRMS Calcd for $C_{21}H_{19}N_5O_5$: 421.1386, found: 421.1410.

Preparation of MOPCH$_2$OC5Ad (9). Reaction of **6c** (0.62 g, 1.56 mmol), adenine (0.25 g, 1.87 mmol), K_2CO_3 (0.52 g, 3.74 mmol), and catalytic amounts of KI in DMF (15 mL) as described for the preparation of **7** yielded **9** (0.37 g, 52.4%) as a white solid: mp 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.37 (q, 2H), 1.58-1.63 (q, 2H), 1.82-1.89 (q, 2H), 3.43 (t, 2H, J = 6.2 Hz), 4.14 (t, 2H, J = 7.1 Hz), 4.24 (s, 3H), 4.79 (s, 2H), 5.90 (bs, 2H), 6.37 (d, 1H, J = 9.9 Hz), 6.87 (d, 1H, J = 2.1 Hz), 7.66 (d, 1H, J = 2.1 Hz), 7.71 (s, 1H), 8.06 (d, 1H, J = 9.9 Hz), 8.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.37, 29.10, 29.77, 43.74, 61.32, 66.48, 70.11, 105.34, 114.71, 115.27, 119.66, 120.40, 126.52, 132.64, 140.40, 140.96, 143.73, 146.56, 146.91, 150.09, 152.69, 155.38, 160.11; IR (cm^{-1}) 3328, 3147, 3113, 2938, 2858, 1729, 1649, 1595, 1481, 1420, 1313, 1132, 1091, 1044, 917, 829, 742; HRMS Calcd for $C_{23}H_{23}N_5O_5$: 449.1699, found: 449.1905.

Preparation of MOPCH$_2$OC6Ad (10). Reaction of **6d** (0.55 g, 1.34 mmol), adenine (0.22 g, 1.61 mmol), K_2CO_3 (0.44 g, 3.21 mmol), and catalytic amounts of KI in DMF (13 mL) as described for the preparation of **7** yielded **10** (0.28 g, 45.2%) as a white solid: mp 155-156.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.38 (m, 4H), 1.50-1.57 (q, 2H), 1.80-2.01 (q, 2H), 3.42 (t, 2H, J = 6.4 Hz), 4.13 (t, 2H, J = 7.2 Hz), 4.24 (s, 3H), 4.80 (s, 2H), 5.79 (bs, 2H), 6.37 (d, 1H, J = 9.9 Hz), 6.89 (d, 1H, J = 2.2 Hz), 7.66 (d, 1H, J = 2.2 Hz), 7.73 (s, 1H), 8.10 (d, 1H, J = 9.9 Hz), 8.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.64, 26.36, 29.45, 29.96, 40.11, 43.77, 61.32, 66.47, 70.34, 105.40, 114.64, 115.28, 119.68, 120.55, 126.52, 132.61, 140.38, 141.06, 143.75, 146.52, 146.95, 150.09, 152.85, 155.42, 160.12; IR (cm^{-1}) 3321, 3160, 3113, 2932, 2858, 1729, 1649, 1595, 1481, 1420, 1313, 1132, 1091, 1044, 917, 829, 735; HRMS Calcd for $C_{24}H_{25}N_5O_5$: 463.1855, found: 463.1880.

Determination of the percent of hypochromism (%H). All UV spectra were measured under the same condition: 5 $\times 10^{-5}$ M, 20 °C, 5% ethanol in water. The percent of hypochromism (%H) corresponds to an integrated hypochromic effect. The hypochromic effect is defined by the percent of hypochromism (%H) = $[1 - f(\text{MOPCH}_2\text{OCnAd})/f(\text{MOPCH}_2\text{OC3}) + f(\text{AdC3})] \times 100$, where f is the oscillator strength of the transition, *i.e*. a measure of the intensity of absorption $f = 4.32 \times 10^{-9} \int \varepsilon(\lambda)/\lambda^2 \, d\lambda$, where $\varepsilon(\lambda)$ is the molar absorption coefficient. The f values were obtained from optical densities measured at every 2.5 nm by application of the Simpson's rule, as described in precedent publications.[24,25] The percent hypochromism (%H) reflects the stacking of the two chromophores in the molecules and its value is generally considered as a measure of the interactions.

Results and Discussion

Figure 2 compares the electronic absorption spectra of the model MOPCH$_2$OC5Ad (**9**), two references AdeC3 (**2**) and MOPCH$_2$OC3 (**4**), and a 1 : 1 mixture of the two reference compounds. The spectra were recorded at 20 °C in 5% ethanol/water at equimolar concentrations of the chromophores. Pure water could not be used due to the poor solubility of the model compounds in water. The concentrations of the solutions were kept low enough (*ca*. 50 μM) to avoid any intermolecular contribution.[15] The spectrum of the model **9** is characterized by decrease of the absorption intensity at all wavelengths. This hypochromic effect is indeed quite comparable to that observed for the psoralen-DNA complex.[26,27]

As summarized in Table 1, the %H values were calculated in six different regions of the spectrum for the four models **7**-**10**. Inspection of the table indicates that all systems show appreciable hypochromism, which is indicative of substantial intramolecular ring-ring stacking. An interesting point, which needs further investigation, is raised by the comparison of %H for the four models **7**-**10** possessing chains of different lengths. All values are important and remain in the same order. This is good evidence that model compounds **7**-

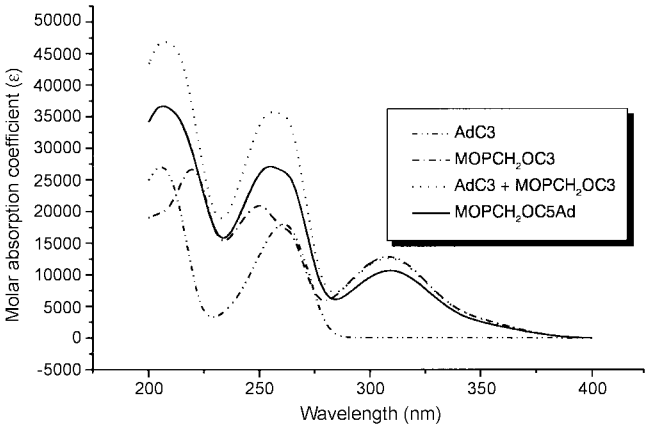


Figure 2. Electronic absorption spectra of MOPCH$_2$OC5Ad **9** (——), AdC3 **2**+MOPCH$_2$OC3 **3** (-----), AdC3 **2** (–·–·–), and MOPCH$_2$OC3 **3** (–·–·–). All the spectra were measured at 20 °C in 5% ethanol/water.

Table 1. Percent hypochromism values (%H) determined for model **7-10** between different wavelength ranges. Spectra measured at 20 °C in 5% ethanol/water. Relative precision of %H is ±0.05%

Wavelength Range (nm)	Model **7** (*n*=2)	**8** (*n*=3)	**9** (*n*=5)	**10** (*n*=6)
400-300	10.42	3.33	4.93	0.96
400-290	13.77	5.40	5.77	1.28
400-260	14.26	6.35	6.88	1.60
400-230	16.85	8.72	8.33	3.48
400-205	17.86	8.95	9.15	4.48
290-230	18.20	5.40	5.77	1.28

10 adopt folded or stacked conformations. The variation of %H values shows significant difference between four and five atoms in bridging chain, but slight difference above five atoms in the linker. These variations probably reflect a decrease of the proportion of folded or stacked conformations as the length of the linker is increased or/and the geometrical overlap of the chromophores in the folded or stacked conformations. For $MOPCH_2OC2Ad$ (**7**) and $MOPCH_2OC3Ad$ (**8**), it turns out that the magnitudes of %H determined for the whole spectrum are quite different, suggesting incomparable degrees of stacking for the two compounds. The large differences observed in the values calculated for the different spectrum portions probably reflect variations in the geometrical overlap of the chromophores in the folded or stacked conformations. This suggests that the complexes adopt different preferred geometries according to the chain length. The model **7** showed the highest value of %H, which allowed the most efficient ring-ring stacking between two aromatic units linked by 3-4 atoms.

We compared the percent hypochromism value (%H) of the model compound **7** ($MOPCH_2OC2Ad$) with that of previously reported model **11** (PsOC3Ad)[15] to study correlation of %H with molecular structures. It is interesting to observe significant difference in %H induced by ring-ring stacking interactions between Ps-Ad and 8-MOP-Ad. The maximum %H values of PsOC3Ad (**11**)[15] were 9.5-13.5, while those of $MOPCH_2OC2Ad$ (**7**) were 10.4-18.2 as shown in Table 1. The results indicate that the 8-methoxypsoralen-adenine systems show more efficient ring-ring stacking interaction than the psoralen-adenine pair. These results could be supported by possible assumptions due to the favorable geometric requirements as follow: (a) The results of MM2 calculation for the models indicate $MOPCH_2OC2Ad$ (**7**) and PsOC3Ad (**11**) to have folded structures so that π-space of adenine is in parallel with that of psoralen. (b) $MOPCH_2OC2Ad$ (**7**) can easily form a hydrogen bond between the 1' amino group and -OCH_3 group because of effective arrangement of two aromatic moieties. Therefore, the structure of $MOPCH_2OC2Ad$ (**7**) is good for ring-ring stacking interaction compared to PsOC3Ad (**11**). These two facts indicated efficient π-π stacking interactions for the model **7**. An energy minimized (by MM2) ball and stick model of **7** is shown in Figure 3.

A particular folded or stacked conformation is intended to portray not necessarily a preferred overlap but rather any stacked conformation.[28] In aqueous solution $MOPCH_2OCn$-Ad can have a number of conformations including unstacked or unfolded and stacked or folded forms. The fluorescence spectra of $MOPCH_2OC2Ad$ (**7**), $MOPCH_2OC3Ad$ (**8**), $MOPCH_2OC5Ad$ (**9**), $MOPCH_2OC6Ad$ (**10**), and 8-MOP (**1**) are measured at the same excitation wavelength (300 nm), and low concentrations (O.D. ≤ 0.34) to avoid self-absorption by any intermolecular contribution and are shown in Figure 4. Although the spectral shapes for all samples are similar, the fluorescence intensity of three model compounds **8**-**10** is stronger than that of 8-MOP. Interestingly, the model **7** (*n*=2) showed much stronger fluorescence than all the other compounds (**8**, **9**, **10**, and 8-MOP) in agree-

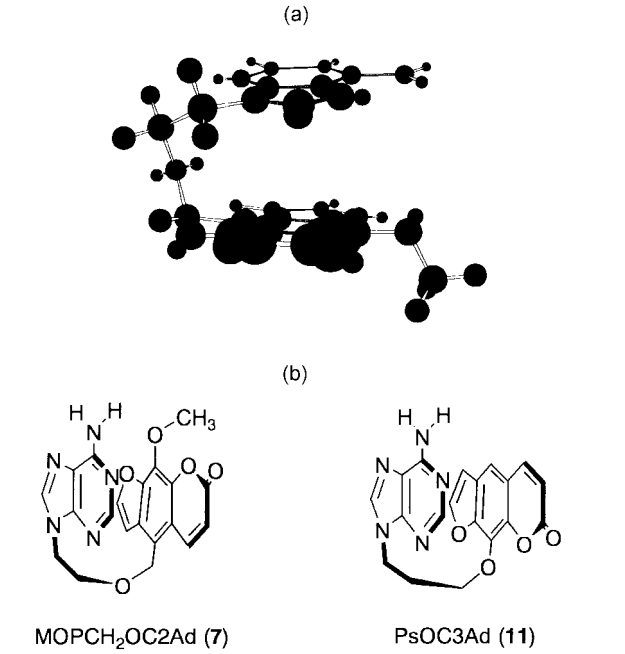


Figure 3. (a) Optimum ball and stick structure for $MOPCH_2OC2Ad$ (**7**) as calculated by MM2 method, (b) The structure of $MOPCH_2OC2Ad$ (**7**) allows intramolecular H-bond different from PsOC3Ad (**11**).

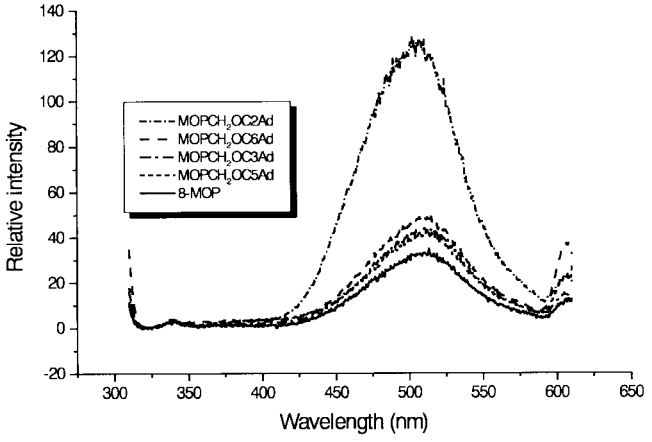


Figure 4. Fluorescence spectra of $MOPCH_2OCnAd$ (*n*=2, 3, 5, and 6) (excitation at 300 nm).

ment with the percent hypochromism (%H) values. The results indicate that 8-MOP and adenine rings in the compound **7** (n=2) are well stacked due to strong π-π stacking interactions resulting in the rigid conformation and consequently the nonradiative decay paths like vibrational relaxation or intersystem crossing are slowed down compare to those in the flexible long linker models **8**-**10** ($n \geq 3$) and 8-MOP.

In conclusion, we have prepared new bifunctional 8-methoxypsoralen-adenine compounds (**7**-**10**) allowing the ring-ring stacking interactions between 8-methoxypsoralen and adenine. Fluorescence and the percent hypochromism studies indicate the most efficient ring-ring stacking interactions in MOPCH$_2$OC2Ad (**7**). In addition, 8-methoxypsoralen-adenine systems show stronger ring-ring stacking interaction than the psoralen-adenine pair.

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